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(54) PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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ABSTRACT:

CLAIMS: Show all claims

*** Note: Data on abstracts and claims is shown in the official language in which it was submitted.

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PROCESS FOR PREPARING SUBSTITUTED PHENYLALKANOIC ACIDS

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This invention relates to novel processes for preparing L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acids.

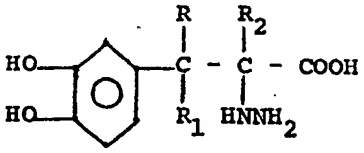
More particularly, this invention relates to processes for preparing L-α-hydrazino-β-(3,4-dihydroxyphenyl)-propionic acids by oxidizing L-α-hydrazino-β-[3(or 4)-hydroxyphenyl]propionic acids.

It is known in the art that various α-hydrazino-β-phenylpropionic acids are useful as decarboxylase inhibitors. It is further known that the D-isomer of these acids is generally inactive and may even be antagonistic to the action of the L-form, thereby reducing its potency.

In the past, it has been the accepted practice to separate stereoisomers by the formation of diastereomeric salts with either optically active bases or acids, depending on the nature of the racemate. However, with the hydrazino compounds of the present invention, separation is complicated by the fact that some diastereomeric salts do not form crystalline materials with sufficiently different properties so that the diastereomers can be readily crystallized. In some instances, the diastereomeric salts are oily or waxy materials which become difficult if not impossible to separate by conventional means. Quite obviously, if a relatively simple and inexpensive process could be found which would preferentially produce the desired L-α-hydrazino-β-phenylpropionic acids, it would receive widespread acceptance in the art.

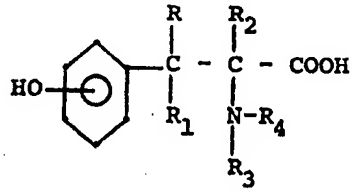
Accordingly, it is an object of this invention to provide a process for the preparation of L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acids. Other objects of this invention will become apparent from the ensuing description.

These objects are accomplished by the present invention which provides a process for the preparation of the L-form of compounds of the formula:



wherein:

R, R_1 and R_2 each may be hydrogen or loweralkyl, which comprises oxidizing the L-form of a compound of the formula:



wherein:

R, R_1 and R_2 are as described above;

R_3 is hydrogen or an acyl radical containing less than about 30 carbon atoms; and

R_4 is NH_2 or $N=R_5$ wherein R_5 is any divalent radical.

The "loweralkyl" radical signifies an alkyl group containing from 1 to about 6 carbon atoms which can be straight chained or branched. The expression "acyl radical" includes any organic radical derived from an organic acid by the removal of the hydroxyl group. It includes such radicals derived from carboxylic acids, sulfonic acids and the like. Protection of the hydrazino function is optional during the oxidation process of this invention. Accordingly, R_4 may be amino or $N=R_5$ in which case the hydrazino function is protected by the provision of a divalent radical such as an imino group, a hydrazone group or a divalent hydrocarbon radical such as methylene, ethylidene, propylidene, benzylidene, and the like.

The oxidation reaction of this invention may be carried out by either biological or chemical means. If it is desired to use biological means, fungi such as Aspergillus ochraceus, Gliocladium deliquescens and Fusarium solani are capable of carrying out the required transformation. It will be obvious to those skilled in the art that isolation of the enzyme system decreases the complexity of the medium, decreases the volume of solutions, solvents and reagents, decreases the labor of isolation and increases the efficiency of conversion.

The oxidation may also be accomplished chemically. By illustration L-α-methyltyrosine is converted to L-α-N^1-acetylhydrazino-α-methyl-β-p-hydroxyphenylpropionic acid. This compound is successively nitrated with tetranitromethane, protected, reduced catalytically with hydrogen over platinum the protected amino compound diazotized and with removal of the protective groups L-α-(3,4-dihydroxybenzyl)-α-hydrazino-propionic acid is obtained.

EXAMPLE 1

L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid

L-α-hydrazino-α-methyl-β-p-hydroxyphenylpropionic acid (1.98 g., 0.01 mole) is exposed to Aspergillus ochraceus in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric acid, extracted with n-butanol and the aqueous phase chromatographed on

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Amberlite-IR-120® on the acid ($H_3\overset{\oplus}{O}$) cycle. Elution with 1 N ammonium hydroxide yields some unchanged starting material followed by L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)-propionic acid. The product is recrystallized from water containing 0.5% sodium bisulfite to yield product, m.p. 208° dec.

EXAMPLE 2

L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid

L-α-methyl-m-tyrosine (97.6 g., 0.5 mole), acetic anhydride (153.1 g., 1.5 moles) and pyridine (200 ml.) are warmed on a water bath at 90-95°C. for 3 hours. The mixture is cooled to room temperature, poured onto 500 g. of ice and extracted with ether. The ether extract is washed successively with water, dilute hydrochloric acid and saturated salt solution. After concentration of the mixture *in vacuo* the residue is recrystallized from acetone-hexane to yield L-O,N-diacetyl-α-methyl-m-tyrosine.

To a slurry of L-O,N-diacetyl-α-methyl-m-tyrosine (111.7 g., 0.4 mole), water (200 ml.), concentrated hydrochloric acid (56.5 ml.) and 320 ml. of ether is added dropwise at 0-10° with vigorous stirring sodium nitrile (29.0 g., 0.42 mole) in water (56.5 ml.). The temperature is maintained at 0-10° during the addition and 1 hour additional stirring. The ether layer is separated and the water layer extracted with two 200 ml. portions of ether. The combined

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ethereal extract is washed with saturated salt solution and dried ($MgSO_4$). The mixture is concentrated in vacuo to yield L-N,O-diacetyl-N-nitroso-α-methyl-m-tyrosine.

A mixture of zinc dust (105 g., 1.6 moles in water (160 ml.) is stirred and cooled to 10°. The nitroso compound of the previous step in glacial acetic acid (240 ml.) is added while maintaining the temperature at 10-15°. After the addition is finished the mixture is allowed to warm to room temperature over an hour and then warmed to 80° with stirring on the steam bath. The mixture is filtered to remove unreacted zinc and the precipitate washed with three 40 ml. portions of warm 2 N hydrochloric acid. The combined filtrate is cooled to room temperature and with cooling basified to pH 6.5. The mixture is filtered and the precipitate dried to yield L-α-(N^1-acetylhydrazino)-α-methyl-β-(3-acetoxyphenyl)propionic acid.

The acid from the previous step (103 g., 0.35 mole) is refluxed with 6 N hydrochloric acid (500 ml.) for 4 hours. The mixture is concentrated to dryness in vacuo, taken up in methanol and diethylamine added to pH 6.4. The precipitate is separated by filtration, washed with cold water and recrystallized from water containing 0.5 sodium bisulfite to obtain L-α-hydrazino-α-methyl-β-(3-hydroxyphenyl)propionic acid.

L-α-hydrazino-α-methyl-β-(3-hydroxyphenyl)propionic acid (2.10 g., 0.01 mole) is exposed to Gliocladium deliquescens in 65 ml. of soybean dextrose medium. L-ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric

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acid, extracted with n-butanol and the aqueous phase chromatographed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide yields some starting material followed by L-α-hydrazino-α-methyl-β-(3,4-dihydroxyphenyl)propionic acid. The product is recrystallized from water containing 0.5% sodium bisulfite to yield product, m.p. 208° dec.

EXAMPLE 4

L-α-hydrazino-β-(3-4-dihydroxyphenyl)propionic acid

L-tyrosine (90.6 g., 0.5 mole), acetic anhydride (153.1 g., 1.5 moles) and pyridine (200 ml.) are warmed on a water bath at 90-95° for 3 hours. The mixture is cooled to room temperature, poured onto 500 g. of ice and extracted with ether. The ether extract is washed successively with water, dilute hydrochloric acid and saturated salt solution. After concentration of the mixture in vacuo the residue is recrystallized from acetone-hexane to yield L-O,N-diacetyl-p-tyrosine.

To a slurry of L-O,N-diacetyl-p-tyrosine (0.4 mole), water (200 ml.), concentrated hydrochloric acid (56.5 ml.) and 320 ml. of ether is added dropwise at 0-10° with vigorous stirring sodium nitrite (29.0 g., 0.42 mole) in water (56.5 ml.). The temperature is maintained at 0-10° during the addition and 1 hour additional stirring. The ether layer is separated and the water layer extracted with two 200 ml. portions of ether. The combined ethereal extract is washed with saturated salt solution and dried ($MgSO_4$). The mixture is concentrated in vacuo to yield L-N,O-diacetyl-N-nitroso-p-tyrosine.

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A mixture of zinc dust (105 g., 1.6 moles) in water (160 ml.) is stirred and cooled to 10°. The nitroso compound of the previous step in glacial acetic acid (240 ml.) is added while maintaining the temperature at 10-15°. After the addition is finished the mixture is allowed to warm to room temperature over an hour and then warmed to 80° with stirring on the steam bath. The mixture is filtered to remove unreacted zinc and the precipitate washed with three 40 ml. portions of warm 2 N hydrochloric acid. The combined filtrate is cooled to room temperature and with cooling basified to pH 6.5. The mixture is filtered and the precipitate dried to yield L-α-(N^1-acetylhydrazino)-β-(4-acetoxyphenyl)propionic acid.

The acid from the previous step (103 g., 0.35 mole) is refluxed with 6 N hydrochloric acid (500 ml.) for 4 hours. The mixture is concentrated to dryness in vacuo, taken up in methanol and diethylamine added to pH 6.4. The precipitate is separated by filtration, washed with cold water and recrystallized from water containing 0.5 sodium bisulfite to obtain L-α-hydrazino-β-(4-hydroxyphenyl)propionic acid.

L-α-hydrazino-β-(4-hydroxyphenyl)propionic acid (2.10 g., 0.01 mole) is exposed to Gliocladium deliquescens in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric acid, extracted with n-butanol and the aqueous phase chromatographed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide yields some starting material followed by L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acid. The product is recrystallized from water containing 0.5% sodium bisulfite to yield product.

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EXAMPLE 5

L-α,β-dimethyl-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid

A mixture of 3-(p-methoxyphenyl)-2-butanone (314 g., 1.76 moles), potassium cyanide (119.5 g., 1.835 moles), 85% hydrazine hydrate (292 ml.) and water (920 ml.) is stirred vigorously at room temperature for 30 hours. The product D,L-α,β-dimethyl-α-hydrazino-β-(p-methoxyphenyl)propionitrile is washed with water and ether and dried. It is not known whether this product and its derivatives are erythro, threo or mixed configuration.

To a mixture of above hydrazinonitrile (219.3 g., 1.0 mole) in 2 l. of dioxane and 0.5 l. of tetrahydrofuran is added simultaneously L-menthoxyacetylchloride (211 g., 0.95 mole) and triethylamine (133 ml., 0.93 mole). The mixture is stirred at room temperature (25°) overnight. The precipitated salts and solvents are removed and the residual oil crystallized from ethyl acetate-hexane. The crystalline material is crystallized to constant rotation from ethyl-acetate-hexane to yield L-α,β-dimethyl-L-N^2-(menthoxyacetyl-hydrazino-β-(p-methoxyphenyl)propionitrile.

A solution of methanol (50 ml.) and concentrated hydrochloric acid (60 ml.) is saturated at 0 to -10° with hydrogen chloride gas. To the mixture at 0° is added with stirring the above hydrazino-nitrile (8.0 g., 0.0193 mole) and the stirred mixture is allowed to warm to room temperature overnight. The solution is concentrated to dryness in vacuo and the residue dissolved in a mixture of 90 ml. of concentrated hydrochloric acid and 10 ml. of acetic. The mixture is heated in an autoclave at 140° for 1.5 hours.

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The mixture is cooled and again concentrated to dryness. From the residue refluxing methanol is used to leach out the hydrazino acid. The volume is concentrated to 50 ml. and after the addition of 10 ml. of benzene, L-α,β-dimethyl-α-hydrazino-p-hydroxyphenylpropionic acid is obtained by addition of diethylamine to pH 6.5. The product is recrystallized from water containing 0.5% sodium bisulfite and 0.5% Versene®.

The hydrazino acid of the previous steps (2.24 g., 0.01 mole) is exposed to Aspergillus ochraceous in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric acid, extracted with n-butanol and the aqueous phase chromatographed on Amberlite-IR-120® on the ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide yields some unchanged starting material followed by L-α,β-dimethyl-β-(3,4-dihydroxyphenyl)-α-hydrazinopropionic acid.

EXAMPLE 6

L-β-(3,4-dihydroxyphenyl)-α-hydrazino-α,β,β-trimethylpropionic acid

A mixture of 3-(p-methoxyphenyl)-3-methyl-2-butanone (384.6 g., 2.0 moles) ammonium carbonate (140.7 g., 18.2 moles) potassium cyanide (167.5 g., 2.58 moles) water (5 l.) and ethanol (5 l.) is stirred and heated at 55-60° for 42 hours. The mixture is cooled to room temperature (25°) and concentrated in vacuo to 1/2 volume. The product is filtered, washed, dried and recrystallized from methanol water to yield D,L-5-(α,α-dimethyl-p-methoxybenzyl-5-methylhydantoin.

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To the above hydantoin (262.3 g., 1.0 mole) in dimethylsulfoxide (2 l.) is added sodium hydride (46.0 g., 2.0 moles) freed of mineral oil. The mixture is warmed at 50° with stirring until the sodium hydride reacts. The mixture is cooled to room temperature and to it added 2.1 moles of chloramine in ether. After 1 hour at room temperature the mixture is warmed to 80° with stirring and stirred at this temperature for 1 hour. The mixture is concentrated in vacuo to about 1/4 volume, diluted with an equal volume of water and filtered. After drying in air at 50° the precipitate is recrystallized from water to yield D,L-1,3-diamino-5-(α,α-dimethyl-p-methoxybenzyl)-5-methylhydantoin.

The diaminohydantoin (29.23 g., 0.1 mole) of the previous step is refluxed with constant boiling hydrobromic acid (125 ml.) for 3 hours. The mixture is concentrated to near dryness in vacuo, flushed twice with 50 ml. portions of t-butanol, extracted with two 100 ml. portions of ethanol and filtered. After addition of benzene (20 ml.) diethylamine is added to pH 6.4. The mixture is filtered, the precipitate washed with methanol and dried. The residue is dissolved in water, treated with charcoal, filtered through diatomaceous earth, washed and the product, D,L-α-hydrazino-β-(p-hydroxyphenyl)-α,β,β-trimethylpropionic acid, recrystallized, filtered, washed and dried.

The hydrazino acid (5.09 g., 0.02 mole) is exposed to Aspergillus ochraceous in 130 ml. of soybean dextrose medium. L-Ascorbic acid (2.0 g.) is added intermittently over 44 hours in 10 portions. The mixture is extracted with n-butanol and the aqueous phase chromatographed on Amberlite-IR-120® on the ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide yields unchanged D and some L starting material

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followed by L-β-(3,4-dihydroxyphenyl)-α-hydrazino-α,β,β,-trimethylpropionic acid. The product is recrystallized from methanol-water containing 0.5% sodium bisulfite.

EXAMPLE 7

L-α-hydrazino-α-ethyl-β-(3,4-dihydroxyphenyl)propionic acid

L-α-hydrazino-α-ethyl-β-p-hydroxyphenylpropionic acid, (2.23 g., 0.01 mole) is exposed to Aspergillus ochraceus in 65 ml. of soybean dextrose medium. L-Ascorbic acid (1.2 g.) is added intermittently over 44 hours in 5 portions. The mixture is acidified with 6 N hydrochloric acid, extracted with n-butanol and the aqueous phase chromatographed on Amberlite-IR-120® on the acid ($H_3O^{\oplus}$) cycle. Elution with 1 N ammonium hydroxide yields some unchanged starting material followed by L-α-hydrazino-α-ethyl-β-(3,4-dihydroxyphenyl)-propionic acid. The product is recrystallized from water containing 0.5% sodium bisulfite to yield product.

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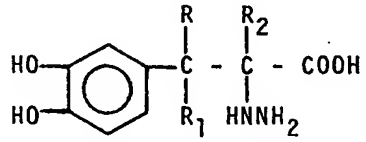
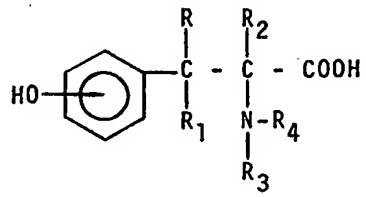
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process for the preparation of the L-form of a compound of the formula:



wherein:

R, R_1 and R_2 each may be hydrogen or loweralkyl, which comprises oxidizing in an aqueous medium with a fungal microorganism selected from *Aspergillus ochraceus, Glioocladium deliquescens* and *Fusarium solani* the L-form of a compound of the formula:



wherein:

R, R_1 and R_2 are as described above;

R_3 is hydrogen; and

R_4 is NH_2, and wherein the hydroxyl group is in the m- or p-position.

2. The process of Claim 1 wherein R is hydrogen, R_1 is hydrogen, R_2 is methyl, R_3 is hydrogen and R_4 is amino.

3. The process of Claim 1 wherein R is methyl, R_1 is hydrogen, R_2 is methyl, R_3 is hydrogen and R_4 is amino.

4. The process of Claim 1 wherein R is hydrogen, R_1 is hydrogen, R_2 is hydrogen, R_3 is hydrogen and R_4 is amino.

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ABSTRACT OF THE DISCLOSURE

Process for preparing L-α-hydrazino-β-(3,4-dihydroxyphenyl)propionic acids by the oxidation of L-α-hydrazino-β-/3(or 4)-hydroxyphenyl/propionic acid compounds. The oxidation is carried out in an aqueous medium in the presence of a fungal microorganism selected from *Aspergillus ochraceus*, *Gliocladium deliquescens* and *Fusarium solani*.